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**Re: Draft Guidance for Industry on BACPAC I: Research Laboratories  
Intermediates in Drug Substance Synthesis: Bulk  
Actives Postapproval Changes: Chemistry,  
Manufacturing and Controls Documentation  
Docket No. 98D-0994**

Merck & Co., Inc, is a leading worldwide, human health product company, that invests more than \$1 Billion on Research and Development (R&D), annually.

Merck's global business strategy is to make our products available to patients and other consumers in many countries, at the same time. This strategy relies on our own R&D pipeline to be prolific and efficient. At the same time, we must rely on regulatory authorities who certify the quality, effectiveness and safety of our products, to administer public policies that are scientifically sound and reasonably predictable, as well as economically and socially responsible. We are prepared to live up to the highest of standards and we challenge our research partners and our competition to do the same.

Merck Research & Development laboratories considers BACPAC I as providing substantial regulatory relief with regard to changes up to and including the final intermediate step. The guidance contains sufficient detail that regulatory decisions are now much clearer for post-approval changes made in early synthetic steps. The general approach of comparing the equivalence of material pre- and post-change represents a rational, scientific method for evaluation of the impact of a given change. The filing requirements in the draft guidance reflect the results of this evaluation and provide considerable regulatory relief from those currently delineated in 21 CFR 314.70. Significant benefit to industry is also realized with the ability to demonstrate equivalence based on the impurity profile of synthetic intermediates after the change, without always requiring evaluation of the API (e.g. physical properties or stability).

It is acknowledged that for many older processes, analytical methodology is not currently in place for full characterization of the impurity profiles of synthetic intermediates. In such cases, the development and validation of adequate analytical methods for quantifying existing and new impurities may be considered too costly to take advantage of the regulatory relief offered by evaluation of changes at process intermediates. For recent and future filings, more detailed in-process specifications and test methods are available and evaluation of changes will be effectively carried out early in the synthesis with these tools.

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## **General Comments**

The following discussion briefly summarizes the key issues from our review of this draft guidance. A detailed list of comments (with reference to specific line numbers) is also provided.

We understand the changes covered by BACPAC I to be within the stated intent of 21 *CFR* 314.70(a), which would encompass changes in the information filed in the approved application. For example, details regarding equipment used in early steps or process scale are not always included in regulatory filings. It is recommended that the section on scale changes be dropped, since the majority of scale changes are driven by changes in equipment or site, which are handled in other sections of the guidance.

One area of concern is the level of documentation requested in support of changes. In some areas, the required data and information are greater than that provided in an NDA filing. In original NDA filings, analytical methods for raw materials and intermediates are briefly summarized and no accompanying validation data are typically. The in-process methods are validated for their intended use and the detailed validation data would be available for inspection. The requirement of certificates of analysis for raw materials and starting materials is another example of additional detail not typically provided. A batch data summary for the relevant materials should meet the requirement. In the case of the redefinition of an intermediate as a starting material, the list of sources and the change-control protocol are considered GMP considerations that should not be included in a filing, but rather should be available for an inspection.

Clarification of what criteria should be used to assess the adequacy of an analytical method for impurity profile analysis would be helpful. If test methods are developed and used for this assessment, it was not clear if they become regulatory methods with accompanying specifications.

The extent of the comparison to demonstrate equivalence of pre-change (10 batches) and post-change (3 batches) material has been clearly indicated. It is suggested that the number of pre-change batches be indicated as “ten or more, if possible”. For certain low volume or recently approved drug substances, the historical database may not include ten commercial scale batches. In such cases, the firm should be allowed to provide justification for the use of less than ten historical batches and/or be permitted to use pilot scale, development and clinical batches. If the use of statistical limits is not feasible, a direct comparison of data should be permissible.

When the assessment extends to the drug substance, the need for physical property evaluation should not include cases where impurity profile equivalence is demonstrated at the crude drug substance prior to a step involving complete dissolution of the material.

Given that this guidance only deals with changes up to the final intermediate, some changes in the indicated type of filings are suggested. An Annual Report is suggested for

site changes to a site that is currently manufacturing/testing a FDA-approved product/intermediate, which uses a similar process or technology, and that has a current satisfactory GMP inspection by FDA or a governmental authority recognized by FDA. If the only change made is a change in specifications driven by an analytical method change to an equivalent or better method, filing in an Annual Report is considered appropriate.

For manufacturing process changes where equivalence is demonstrated prior to the final intermediate, the relative risk of such a change is very low given the subsequent processing. Therefore, process changes for which equivalency is shown before or at the final intermediate are suggested as Annual Report filings. Where equivalence was not shown until the final drug substance, a Changes Being Effectuated supplement could be the filing mechanism.

### **Specific Comments**

The following represent specific comments on specific text (designated by line) of the draft guidance document. Comments have been grouped as major, minor or clarification through changes in wording. When a comment applies to a section that is repeated several times in the document (i.e. Test Documentation), the comment is shown with the first line of text that it refers to and subsequent lines of the same text are referenced. Text that is suggested for addition is generally underlined to differentiate it from existing wording.

#### **I. Introduction**

##### *Major Comments*

Line 16 It is noted that the scope of BACPAC I includes changes “... *involving the synthetic steps up to and including the final intermediate.*<sup>4</sup>...”. The referenced footnote 4 notes: “<sup>4</sup> *Changes to the final intermediate and manufacturing changes after the final intermediate will be covered in a forthcoming BACPAC II guidance.*” These statements appear to be misaligned as it looks like the final intermediate is covered by both BACPAC I and BACPAC II. Footnote 4 should be modified to read “<sup>4</sup> *Changes*” ***subsequent*** “*to the final intermediate...*”

#### **II. General Considerations**

##### *Major Comment*

Line 120-121 Replace the sentence: “When new methods are developed for this purpose, validation data should be provided” with New methods that are developed should be appropriately validated for the intended purpose and the validation data should be available for inspection.

### III. Assessment of Change

#### A. Equivalence of Impurity Profiles

##### *Minor Comments*

Line 124      Modify “ten or more premodification (may include pilot scale, development and clinical) ~~commercial~~ batches.

In addition, can an alternate comparative database be proposed for the number of premodification batches in the event that the material was manufactured infrequently or if changes had occurred in the manufacturing history which may support a reduced data set as being most appropriate for comparison?

Line 129      It is suggested that the demonstration of equivalence may take place at an *in situ* intermediate, if appropriate justification is provided, and that the line should read isolated (*in situ*, if appropriately justified). (also applies to line 159)

Line 132      To comply with ICH, delete “at or” since unspecified impurities above 0.1% are the issue.

Line 137      Modify to include any specifications for specific impurities that have been filed for an intermediate:

Existing impurities, including residual organic solvents, if relevant, are within the stated limits or, if not specified, at or below the upper statistical limits of historical data.

Line 139      Modify to include specification for total impurities that has been filed for an intermediate:

*Total impurities* are within the stated limits or, if not specified, at or below the upper statistical limit of historical data.

#### B. Equivalence of Physical Properties

##### *Major Comments*

Line 191      If impurity profile equivalence is demonstrated at the crude drug substance stage then physical property evaluation should not be required. Suggest change from “prior to or at the final intermediate” to “prior to the final API”.

Line 200      Add the underlined text:

Conformance to historical particle size distribution profile, when acceptance criteria do not exist.

## **IV. Types of Changes**

### **A. Site, Scale, and Equipment Changes**

#### **1. Site Changes**

##### *Major Comments*

Line 234 Include information regarding the current status of site for manufacturing/testing a FDA-approved product/intermediate which uses a similar process or technology, and if the site has a current satisfactory GMP inspection by FDA or a governmental authority recognized by FDA.

Line 241 Indicate brief description of analytical methods, since for intermediate testing only a short summary of type of method and conditions is typically provided in the NDA. (also applies to lines 287, 346, 372, 415, 454 and 508)

Lines 243-245 For in-process tests or tests on intermediates, validation data are not routinely included in the NDA filing. It is suggested that the sentence “Validation data should be provided for new test methods and also for existing methods if their use is being extended beyond their original purpose” be replaced with These methods should be appropriately validated. This evaluation will not necessarily result in additional specifications or testing requirements. (also applies to lines 289, 333, 348, 375, 417, 456 and 511)

Lines 259-260 The requirement for a certificate of analysis for each outsourced intermediate could also be addressed by a compilation of batch data. (also applies to lines 259, 305, 391, 439, 477 and 534)

##### *Minor Comment*

Lines 262-272 It is suggested that an Annual Report be the filing for a change to a site that meets the following criteria:

- currently manufacturing/testing a FDA-approved product/intermediate, which uses a similar process or technology
- current satisfactory GMP inspection by FDA or a governmental authority recognized by FDA.

#### **2. Scale Changes**

##### *Major Comments*

It is recommended that scale changes not be included as a separate category, since other changes handled elsewhere in this guidance (i.e. equipment or site) typically accompany scale changes.

### **3. Equipment Changes**

#### *Major Comments*

Line 314 Even exact replacement of equipment may require some minor adjustment of processing parameters. Change as follows, “used with only minor ~~no~~-modifications to processing parameters.”

#### **A. Specification Changes**

##### *Major Comments*

Lines 330-334 It is our understanding that test methods involved in compendia changes have been validated by the proposing agency, i.e. USP. It would seem unnecessary for the filer to repeat the validation or obtain the validation data from the agency. Recommendation is that the phrase “with appropriate data for any new analytical method used” be deleted from lines 333-334.

Lines 349-350 and line 391 Inclusion of CoA’s for raw materials and solvents is not considered necessary based on the early stage of the synthetic process. Batch data for intermediates should appropriately address this item.

Line 354 and line 395 If the only change made is a specification change, then reporting by Annual Report is considered appropriate. Also for deleting a test or replacing an analytical method, supporting impurity profile documentation may not be appropriate. If another type of change were also made (i.e. manufacturing process) that led to the specification change, then evaluation of equivalence would need to be demonstrated and the designated filing mechanism used.

##### *Minor Comments*

Line 370 Delete physical properties testing for assessment of intermediates.

Line 332 The filing documentation is given as “Annual Report” in. The phrase “or supplement” in line 332 is in contradiction with this. Recommendation is that the phrase be deleted from line 332.

#### **B. Manufacturing Process Changes**

##### *Major Comments*

Line 442 For manufacturing process changes made prior to the isolated final intermediate, reporting by an Annual Report is suggested for all cases where impurity profile equivalence is demonstrated before or at the final intermediate. For those changes in which the evaluation is carried out on the drug substance, a Changes Being Effected supplement is the suggested filing.

Lines 501-502 “A list of sources of the redefined starting material” is considered a GMP item that should be available for inspection, but not be included in a filing to the agency.

Lines 503-505 The change-control protocol is another GMP requirement that should be available during an inspection, but should not be required to be filed with the agency.

Line 95-96 This issue involves how a drug substance is defined. For example, the drug substance may be defined as a 1:1 racemic mixture or be a single enantiomer/diastereomer which contains the other enantiomer/diastereomers as low level impurities. In the case of low level isomeric impurities, the change could result in a decrease in the level of the undesired isomer and the resulting material could still be considered equivalent or better.

Suggested revision: demonstrate equivalence (e.g. chirality). ~~For example, if the drug substance is a mixture of isomers, then the same quantitative mixture should be obtained after the change.~~

Line 103 Substitute may for “should”. (also applies to lines 257, 303, 389, 437, 475 and 532)

Line 115-116 For changes made prior to or at the final intermediate, the option should be available for a firm to choose not to evaluate the impurity profile at an intermediate, but instead do the evaluation at the drug substance.

Line 131 After “1. An intermediate:” add The applicant may evaluate any subsequent intermediate or the final API to confirm if impurity levels comply with this guideline.

Line 227 Change “single facility” to contiguous campus.

Line 311 Modify to “when equipment (as specified in the filing) changes alone are made”.

Line 319 Change “previously used” to “previously filed”.

Line 323 Add the phrase “significant change of equipment from that previously filed.”

Line 325 Delete the final phrase “and documented as described for scale changes” since we have suggested deletion of that section.

Line 413 and 452 Delete physical properties testing for assessment of intermediates.

Lines 420-421 If equivalence of the impurity profile is established prior to the drug substance (even at the stage of crude API) then no physical properties testing of the drug substance should be necessary. (see comment on line 191)

### Clarification

Line 86 Notes the need for assessment of stability should be considered. Does this mean stability of the drug substance, drug product, or both?

Lines 116-117 Notes that testing can be carried out on the drug substance itself. To be clear, is this the same way of saying that the intermediate can be brought forward to the final drug substance – in other words a use test? Can this use test be conducted on a lab, pilot or full scale basis?

Line 126 What is the definition of “no trend”? Is there a statistical significance which is acceptable?

Lines 139 and 153 “...upper statistical limit...” should be defined.

Lines 168 Does the term “Pilot Scale” include material made at a laboratory scale that meets the definition of “representative of and simulating”?

Lines 218-220 & 227-228 Clarity is needed with respect to single manufacturing facility, contiguous campus, etc.

Line 221 The term “environmental controls” should be clarified. Does this refer to processing environment or to emissions, etc?

Line 89-91 Rephrase as:

For such drug products ~~in which stability problems may potentially occur~~, the first commercial *batch* of drug product made with postchange drug substance may be included in the firm’s stability testing program.

## **Attachment B – Glossary of Terms**

Line 571 Replace “processed” with produced.

Line 576 Add “Drug Substance (API)”.

Line 582 Add “covalent bond formation and/or cleavage”.

Line 585 Clarify “The step that includes solution”.

Line 589 Revise to “impurities or physical attributes (for API) from 10 or more recent batches, representative of the established process, of the intermediate or API at the point where the firm is attempting to establish equivalence”.

Line 591 Revise to “(~~The appropriate review division(s) should be contacted for concurrence~~ Written justification should be provided in those ~~rare~~ instances”.

Lines 607-608 Delete the sentence “The isolation or purification procedure should be part of the validated process.” This sentence is not relevant to the definition.

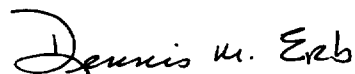
Line 633      Replace “drug substance” with material, since in BACPAC I many evaluations cover intermediates.

Lines 640-643      Align term and its definition with ICH Q7 (in working group) as follows:

API Starting Material: A material used in the production of an API which is itself or is incorporated as a significant structural fragment into the structure of the API. A starting material may be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or it may be produced in-house. Starting materials are normally of defined chemical properties and structure.


We appreciate the opportunity to comment on this draft guidance.

Sincerely,

A handwritten signature in black ink that reads "Dennis M. Erb". The signature is fluid and cursive, with the first name "Dennis" being the most prominent part.

Dennis M. Erb, Ph.D.  
Senior Director  
Regulatory Affairs

Q/ligi/guidance/bacpac

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